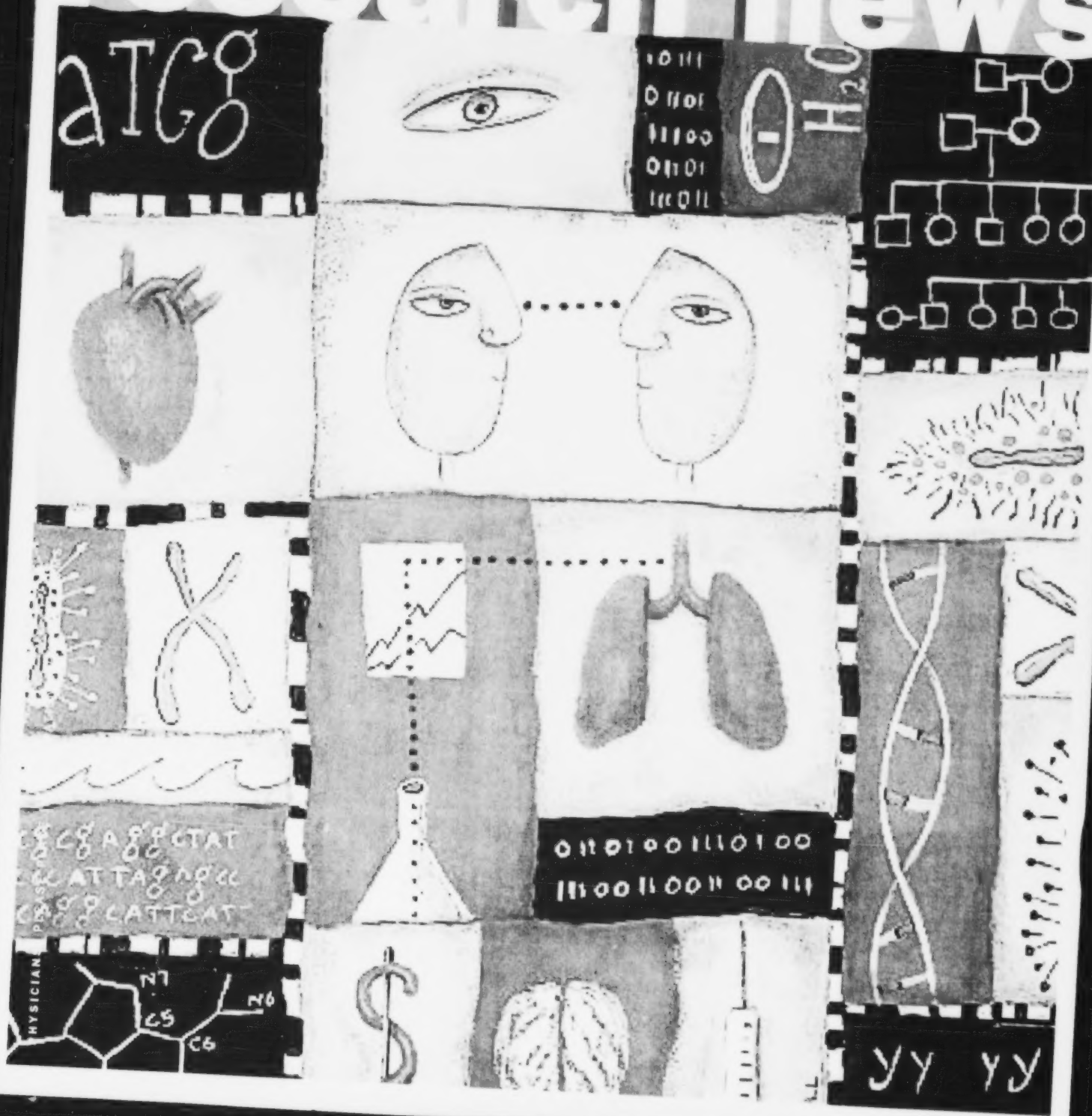
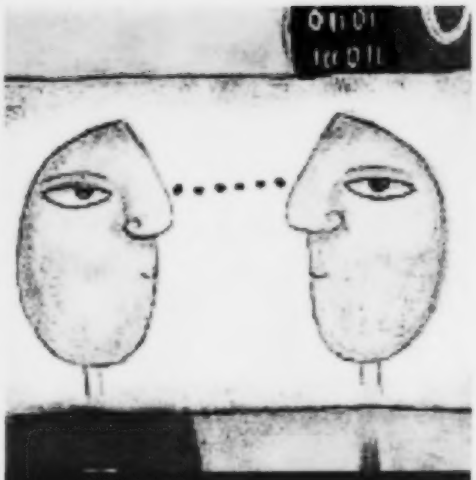
ALBERTA HERITAGE FOUNDATION FOR MEDICAL RESEARCH

ahfmr research news

SPRING 2000





research news

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AHFMR Mission

AHFMR supports a community of researchers who generate knowledge that improves the health and quality of life of Albertans and people throughout the world. AHFMR's long-term commitment is to fund basic, patient and health research based on international standards of excellence and carried out by new and established investigators and researchers in training.

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Research Views

Dr. Michael Smith

Dr. Smith, like many research scientists, feels that patenting genes is counter- productive. Scientists, never mind patent offices, don't know what many of the genes with patents pending, actually "do". Then there is the debate about what knowledge should remain in the public domain. Dr. Smith points out an analogy:

"Patents do not exist on our bones, yet pharmaceutical companies have profited greatly from technologies, developed from basic bone research, that combat osteoporosis and other bone conditions. Analogously, patenting genes is like patenting bones. It is the products of genes, the proteins, that make us human, make us individual, and are a key component in the total picture of human health. There is lots of room for companies to benefit from legitimate commercial interests when the functions of genes and proteins are known through research."

What is most worrying, the patenting of genes could also inhibit genetics research, which, like all basic research, is the pathway to future human health. The use of genetics is also a hot topic of debate globally. Dr. Smith emphasizes the necessity of having the right framework of testing and regulations in place, one that keeps up with the use of genetics or any new technology.

Canada is a leader in genetics research due, as Dr. Smith points out, to several factors. "Canada has excellent researchers and clinical geneticists, among them Dr. Diane Cox, the discoverer of Wilson disease and Chair of the University of Alberta's Department of Medical Genetics, which was funded in part by AHFMR. Canada also has isolated pockets of populations that have retained similar genetics through the decades. Extended, linked families in Newfoundland, for example, are an enormous resource for genetic researchers."

Federal funding is also fuelling Canada's achievements. "Canada is in a position to compete internationally in the genetics field through the support of the Canada Foundation for Innovation, the 21st Century Chairs for Research Excellence Program, and the Genome Canada Program. We have an opportunity to build up the calibre of genomics research all the way from pathogens to humans."

Once the human genome—all 100,000 genes of it—are identified within the next year, an even more daunting task begins, says Dr. Smith. "The next step is identifying the differences in the same genes in people. It is estimated that the frequency of difference between two people occurs in about every 1000 base pairs of the nucleotide building blocks that make up genes. [There are about 3000 million base pairs in human chromosomes.] When the same base pair differs in two people, it is called single nucleotide polymorphism.

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diagram to come

If we can identify, for example, a gene for a type of cancer, and track how the base pairs in this gene differ from person to person, these variations can help us answer why some of us are resistant to, or at risk for the disease. We could then tailor-make therapies based on each person's DNA."

"Currently the National Institutes of Health in the U.S., the Wellcome Trust in the U.K., and a consortium of large pharmaceutical companies are working on a single nucleotide polymorphism project. It should be complete in two or three years. Perhaps in the future, epidemiologists together with laboratory scientists can map out the possible health risks of a particular population, given that genes are just one component of health, along with nutrition and other factors.

"Proteomics, the analysis of the function and relationship of the proteins expressed by genes, will have a huge impact on human health. Currently we can look at individual proteins or small clusters of proteins and see what they do. But proteomics is concerned with how all proteins work individually and in relationship with each other, a Herculean task that requires technology that has yet to be developed."

In spite of all the advances in genetics technologies, one of the original approaches in the field underpins modern genetics research. Dr. Smith relates, "In 1976, Dr. Sanger developed a completely new technology to make our task of sequencing the viral genome possible. Suddenly we knew a lot more about the virus than classical biology could tell us, leading to a quantum advance in biology. Even though computer advances have increased light years from then, Sanger's technology is still the basis of modern DNA sequencing. It is interesting to see how far a good idea can be pushed out from its initial application."

Dr. Smith is the founding Director of the Genome Sequence Centre at the B.C. Cancer Agency in Vancouver. He divides his time between the Centre and the University of British Columbia where he is a University Killam Professor and Peter Wall Distinguished Professor of Biotechnology. Dr. Smith was one of the distinguished members of AHFMR's third International Board of Review convened in 1998 to report on the activities of the Foundation during the previous six years.

DR. DELE DAVIES

DR. GORDON FRANCIS

$43 million for AHFMR research

Dr. Dele Davies is investigating the potential development of a vaccine against Group B strep, which can cause serious illness or death in newborn infants if not treated. Dr. Gordon Francis is researching the modification of HDL, the "good cholesterol", as a potential heart therapy. Dr. Kathleen Hegadoren studies the risk for depression in women and factors that influence treatment. These three researchers—two physicians and a nurse—belong to a select cadre of scientists in Alberta who can call themselves Heritage researchers.

These three are among 61 outstanding researchers who have been offered nearly $43 million through this year's AHFMR Biomedical and Health Personnel Awards competition. This is the largest amount ever awarded to researchers in AHFMR's 20-year history and represents an 11% increase from last year. The awards are offered to people in 13 different faculties at the University of Alberta, the University of Calgary, and the University of Lethbridge.

It's not easy to become a Heritage researcher. AHFMR's global peer-review system is formidable. And, as with any competition, the strengths of a given pool of applications set the level of achievement for all. Over the past two decades, AHFMR's standards of excellence have led to the province's current profile as a major centre for biomedical and health research.

Health Research Fund awards announcement

Health Research Fund (HRF) projects provide vital information about important questions in the fields of health services, population health, mental health, and health technology assessment.

This year, AHFMR has awarded more than $1.48 million to 20 two-year research projects throughout the province. Projects focus on such subjects as the genetic risk for spine and hip disorders, health beliefs of insular communities, and ways of improving access to care for schizophrenics.

A further $700,000 will be granted to researchers conducting ongoing projects approved in last year's competition. The Health Research Fund is administered by AHFMR for Alberta Health and Wellness through a contractual arrangement.

info:

For a listing of Year 2000 AHFMR Senior Personnel Awards, please go to the AHFMR Web site at http://www.ahfmr.ab.ca/grants/awardlist2000.html

For a listing of Year 2000 Health Research Fund projects please go to the AHFMR Web site at http://www.ahfmr.ab.ca/grants/guidelines.html

The Launching

When the Alberta Heritage Foundation for Medical Research was established in 1980, there was nothing like it in the world. With an endowment of $300 million from the Heritage Savings Trust Fund (established in 1975), and an initial plan to eventually spend about $30 million a year from the interest revenue, Alberta was investing more money per capita in medical research than any other province in the world.

The Foundation was born of extraordinary circumstances—unprecedented wealth from oil and gas sales as a result of the OPEC crisis—and a far-sighted vision, that of Premier Peter Lougheed and his government. He was determined Alberta would think pan-Canadian and become a leading province in many areas, with a newly diversified economy that included what he called "brain industries".

He recalls: "We thought we should do a few things that are extraordinary, that couldn't be done by governments under normal circumstances. Could we make a long-term investment in some area that would produce long-term results—not just for Albertans, but for the world?"

While the Cabinet cast around for the right initiatives, delegations from the medical schools at the Universities of Alberta and Calgary made a modest, relatively short-term proposal for research funding. The concept matched provincial goals for raising the standard of Alberta's health and education systems and fit the larger vision, but the Government was thinking much bigger.

It decided to establish a funding agency unlike any other, so the Premier appointed special advisor Dr. Jack Bradley to ask national and international leaders in the field of medical research what a world-class agency should look like.

Elsewhere, medical-research funding agencies had experienced the fallout of annual budget appropriations tied to variable, short-term, political agendas of the governments of the day. The failed "war on cancer" in the United States was a striking example. The Alberta Government decided that the Foundation must be at arms'-length from government.

The Government agreed that all funding decisions would be made by trustees, who would report to the Legislature annually. Treasury would manage the endowment, and Foundation trustees could access whatever funds they required on a regular basis. Successive governments have maintained the arms-length relationship. That's because there is a carefully layered structure for accountability.

First, the Foundation is advised on all major initiatives by an international Scientific Advisory Council. Funding is allocated through a solid peer review system, in which applications are judged by external, established scientists to maintain international standards of excellence. Every six years, the Foundation is externally assessed by an International Board of Review (IBR). In 1980, Premier Lougheed made it clear the future of the Foundation depended on its report card after the first six years.

# of AHFMR

There was, however, much debate about what kind of medical research the Foundation should support. The mandate was to support "a balanced long-term program of medical research", referring to a field and not a profession, and to a balance between basic and clinical research, but how was this to be defined? (It's a question still asked today).

In 1979, few non-researchers understood how molecular biology and genetics were about to revolutionize our understanding of disease. Or the importance of social and economic factors to health. Finally, acting on advice from leading scientists abroad and at home, the Government directed the Foundation to focus on excellence in basic science and, as that became established, consider clinical and other health research. The carefully worded AHFMR Legislative Act provided direction, but allowed the Foundation to respond to changing times and scientific progress by offering new programs and modifying existing ones.

Alberta would think pan-Canadian and become a leading province in many areas, with a newly diversified economy that included what Premier Lougheed called "brain industries".

Early in 1980, the A.H.F.M.R. Act was proclaimed and two months later, Dr. Jack Bradley became Executive Director, and Mr. Eric Geddes, former chair of the Board of Governors at the University of Alberta, was appointed Chair of the Board of Trustees*.

If any of the new trustees had private doubts about the Foundation's arms-length relationship and the scope of their responsibilities, they soon learned the score at a breakfast hosted by the Premier at Government House Mr. Geddes recalls: "The message was very simple from Premier Lougheed. He started the meeting by saying, 'This is the last time I will ever meet with you', then quickened to say, 'which doesn't mean that I'm not available for counsel.' He wanted to make the point that the trustees were being entrusted with the entire responsibility for the Foundation and there would be little, if any, political interference."

The Government kept its promise of total independence and the trustees lived up to the daunting challenge. The first scientific awards were handed out in the fall of 1980 to students and fellows. (An early priority was to build training programs, providing new opportunities for young Albertans and other Canadians.) In early 1981, Dr. Lionel McLeod, then Dean of Medicine at the University of Calgary, became the Foundation's first President. That same year, the first senior scientists were recruited, showing skeptics that, yes, scientists would move to Alberta from Toronto, Montreal, Paris, Cambridge, Boston, Auckland or Tokyo. They were attracted by the generous funding, protected time for research, relative freedom to pursue their ideas, and the opportunity to work in a growing community of dynamic scientists. They still come for the same reasons.

The Foundation was well launched, to the envy of other Canadian provinces and many foreign jurisdictions, who waited to see if the bold venture would work. Could Alberta really become a world centre of medical research?

Most definitely it could. In 1987, the first IBR gave the Foundation a glowing report card, declaring that its "programs have produced a unique medical research milieu that is likely not matched elsewhere in the world." Two decades after the launch, the third IBR gave equal praise. One 1999 IBR member, Nobel Laureate Dr. Michel Smith, called the Foundation a national treasure, adding "Long may it flourish."

The founding trustees were: Eric A. Geddes (Chair), William Daniel Dickie, Robert Robertson Francis, Myer Horowitz, N. Patrick Lawrence, LeRoy Harding le Riche, Michael Brien O'Byrne, Gordon Cummings Swann, Norman Ernest Wagner.

Scientists discover new gene associated with Alzheimer's. Research zeroes in on gene for mental illness. New gene linked to breast, lung cancer.

A new crystal ball?

It seems as though almost weekly there's news about another discovery of a gene that is related to a serious disease. Since we now know how to identify mutations (changes in genes) that lead to certain disorders, we've opened up the possibility of genetic testing.

However, although we can do the tests, we don't necessarily know what to do with the results.

There are a great many personal, legal, ethical, and educational concerns associated with genetic testing. Many of the mutations currently identified do not provide a definitive answer about whether or when a person will actually get a disease. Another major consideration is that we can not yet cure many of the diseases we can test. In these cases, the benefit of finding out about a predisposition to a disease is highly questionable.

"We've got to get this right," sa Heritage researcher Prof. Tim Caulfield, a lawyer and the Research Director of the University of Alberta's Health Law Institute. "We're now at the stage where genetic research is beginning to be commercialized, and research results are being put to practical uses like genetic testing. We must learn how to reap the benefits and mitigate concerns."

Cutting through the hype

One of Professor Caulfield's major research areas is genetics, ethics, and the law. As an AHFMR Population Health Investigator, he is working on a three-year project studying legal issues in the allocation and utilization of genetic services.

"There's been a lot of talk about the commercialization of genetic research. Unfortunately, much of it is hyperbole rather than discussion of the real issues," says Professor Caulfield. "We see a focus on eugenics, the science of manipulating the human genome in order to improve the human species. There's talk about passing laws to prevent the cloning of people to be used as organ banks. While there's no doubt that abuses are a possibility, we can't use these science-fiction-type scenarios as our basis for discussion.

"The hype is a disservice to the depth of scientific knowledge. It hinders us all from talking about the real issues, such as genetic testing."

Enter the Canadian Biotechnology Advisory Committee (CBAC), which was created in 1999 to provide independent advice to seven federal ministries on issues related to the development and application of biotechnology. Professor Caulfield is one of CBAC's 21 members, who come from the scientific, business, ethical, and environmental communities, as well as from the general public. An important element of CBAC's mandate is to raise public awareness about these issues among Canadians.

"Genetics is complex, its impact is complex, and we've really only started to debate what we can and should do with this knowledge," says Professor Caulfield. "There was once a belief that that we could sort all this out quickly, and we'd never have to talk about it again. I believe that the depth, richness, and enduring quality of the issues ensure that they will never go away.

"Many people don't understand that simply because there is a test for a disease doesn't mean there's a cure for it,"

"We must start to build the regulatory framework now that will allow us to deal with these issues."

A look at the issues

Physically, having a genetic test is just like having any other blood test. But that's where the simplicity ends. The social, legal, and economic implications of genetic testing are very complicated.

One of the most obvious issues is what to do with the results. If a test is negative, it can lift a tremendous burden from a individual. But if a test is positive, the results may be mixed.

"Many people don't understand that simply because there is a test for a disease doesn't mean there's a cure for it," Professor Caulfield says. "A positive test can be very unwelcome news when no effective treatment is available."

In addition, most diseases do not follow simple patterns of inheritance. A positive test does not necessarily mean a person will get the disease – it often means simply that they have a certain increased risk of developing the disease. Many factors influence how a gene works, and who will get a disease and when. For example, some mutations are triggered by environmental exposures. The fact that mutations in several different genes can lead to the same disease further complicates matters.

"This complexity highlights the critical role of genetic counselling," adds Caulfield. "The decision to have a particular test should be an informed one. But research has shown that even the professionals who counsel people are being overwhelmed by genetic information. It's very difficult to keep up.

"If genetic testing is to be available, we absolutely must have counselling in place. Ensuring this should be part of the regulatory process."

In Canada, there are currently no formal policies or regulations specific to genetic testing. (Some existing laws are relevant to genetic testing.) Caulfield supports the development of a regulatory model, similar to what has been done in the United Kingdom. "A laboratory would apply to do a specific genetic test or tests, the application would be reviewed by a regulatory body, and a license issued or withheld.

"The hype over genetic testing has hindered the development of a regulatory process. The debate has focussed on whether a particular test should or shouldn't be allowed. I believe prohibitions should be the last thing we do, not the first thing. We need a flexible, effective regulatory model. Then we can use prohibitions for what we really don't want to do."

"There are no easy answers to these questions," says Professor Caulfield. "That's why we need a public discussion, one that focuses on how the genetic revolution affects our everyday life. Not sometime in the future, but right now.

"I think we are at a crucial time with genetic testing. Companies are already offering genetic-testing services. We need strong regulations that govern marketing, quality control, and the validity of tests. These will go a long way toward bolstering public confidence."

Keeping your genes a secret

Privacy is another key concern. Last year at a U.S. congressional subcommittee hearing, the Director of the National Human Genome Research Institute spoke about the low enrolment in clinical trials studying the breast-cancer gene BRCA. Dr. Francis Collins testified that women are worried that insurers will deny them coverage if they test positive for a mutation.

Individual states, such as California and New York, have passed laws prohibiting insurance discrimination on the basis of genetic test results and services. There is now a move to develop a federal law providing protection at the national level in the United States.

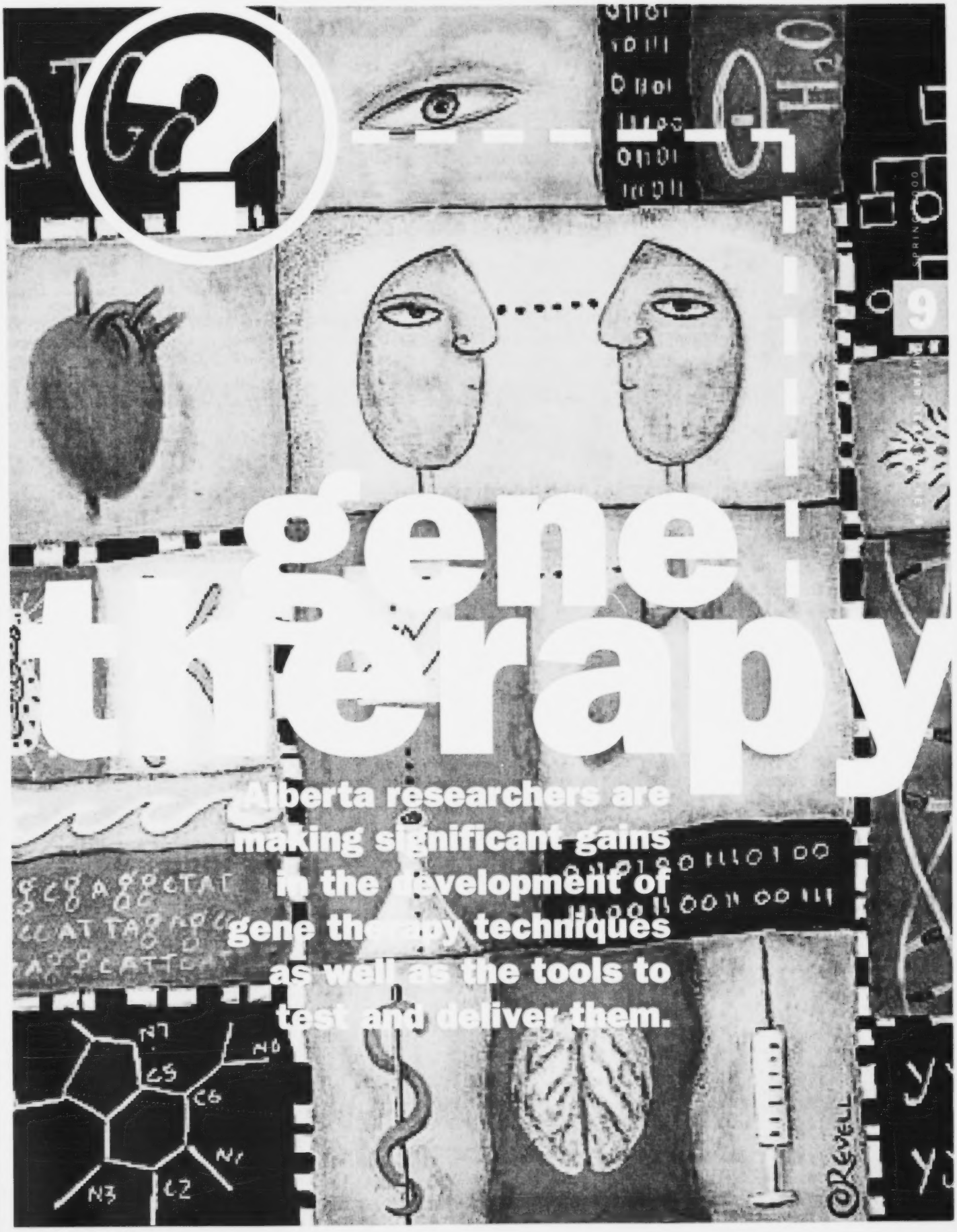
"In Canada, the situation has been somewhat different because the issue of insurance isn't as critical," notes Professor Caulfield. "There are broader concerns, such as patient confidentiality and the obligation of health-care providers to warn others of risk. If a doctor finds that a patient has a mutation that causes a particular illness, is he or she obligated to warn the patient's siblings?"

The decision to have a test or not to have a test can affect many people. Does one have a moral responsibility to know one's genetic condition? To warn family members of their potential susceptibility?

"There are no easy answers to these questions," says Professor Caulfield. "That's why we need a public discussion, one that focuses on how the genetic revolution affects our everyday life. Not sometime in the future, but right now.

"I feel fortunate to be involved in this process. There is so much promise in the incredible amount of knowledge that we now have about genetics. I'm optimistic that the genetic revolution will be a constructive force."

Tim Caulfield is an AHFMR Population Health Investigator, Research Director of the Health Law Institute, and Assistant Professor in Health Law at the University of Alberta.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gene therapy
Alberta researchers are making significant gains in the development of gene therapy techniques as well as the tools to test and deliver them.
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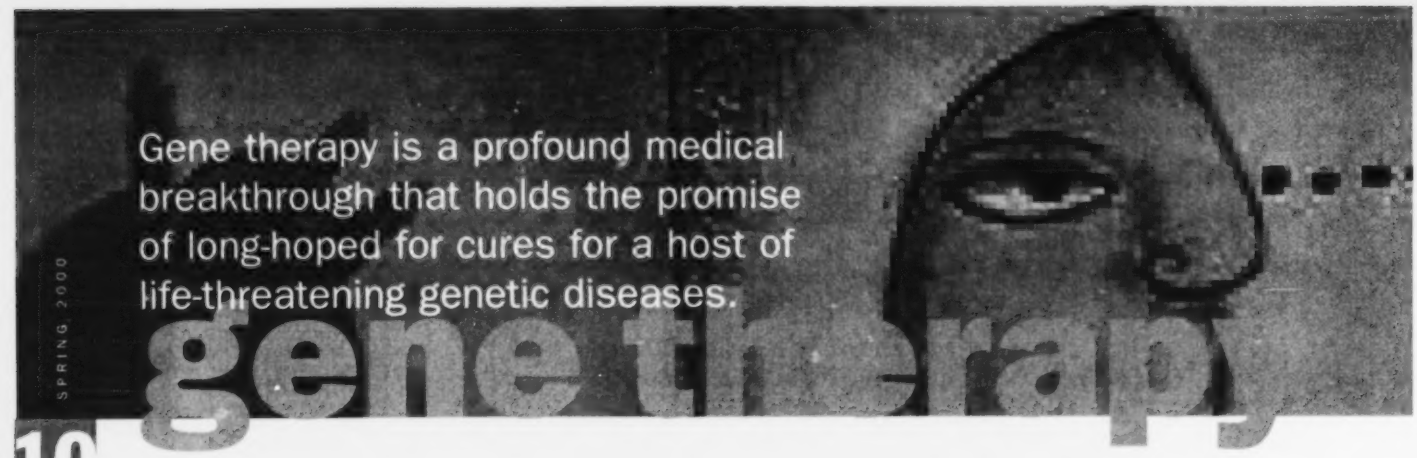
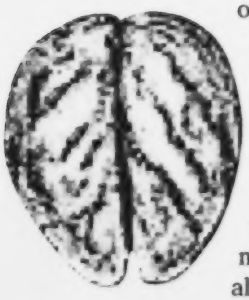


Gene therapy is a profound medical breakthrough that holds the promise of long-hoped for cures for a host of life-threatening genetic diseases.

gene therapy

Increasingly, newspaper stories mark the ever-quickening advances made by researchers working in gene therapy. Recent headlines have heralded promising international developments in this still-experimental field. In the last year, U.S. scientists announced they had found a way to measurably improve the health of severe hemophiliacs by injecting them with a gene that seems to help blood clot. Across the ocean, British researchers said a new gene therapy procedure they had developed could be used to keep arteries open after coronary bypass surgery.



Alberta researchers are making significant gains in the development of gene therapy techniques as well as the tools to test and deliver them.

Researchers in Alberta have kept pace with the breakthroughs. In the latest advance, announced last February, scientists at the University of Alberta told the world that they had successfully used gene therapy to treat rats with asthma. This is a discovery that could eventually mean the end of steroid inhalers to treat asthma attacks. Other Alberta researchers are not far behind. They're making significant gains in the development of gene therapy techniques to treat diabetes and other genetic diseases, as well as providing themselves and fellow scientists with the tools to test out and deliver the new gene therapies they conceive.

Hemophilia, asthma, and heart disease are a small sample of the thousands of genetic diseases and conditions that could soon be impacted by discoveries made in this relatively new and rapidly progressing field. It was only a decade ago that researchers at the U.S. National Institutes of Health performed the first approved gene therapy procedure on a human being, a four-year-old girl with a severe disease that affected her immune system. But the potential for gene therapy has evolved over the past fifty years. Scientists first determined the structure of DNA, then they set to cracking the genetic code, and eventually they developed the means to deliver genes to the cells. Some of the groundwork for successful gene therapy will near completion when the Human Genome Project, an international effort to identify the estimated 100,000 genes that make up human DNA, soon comes to a close.

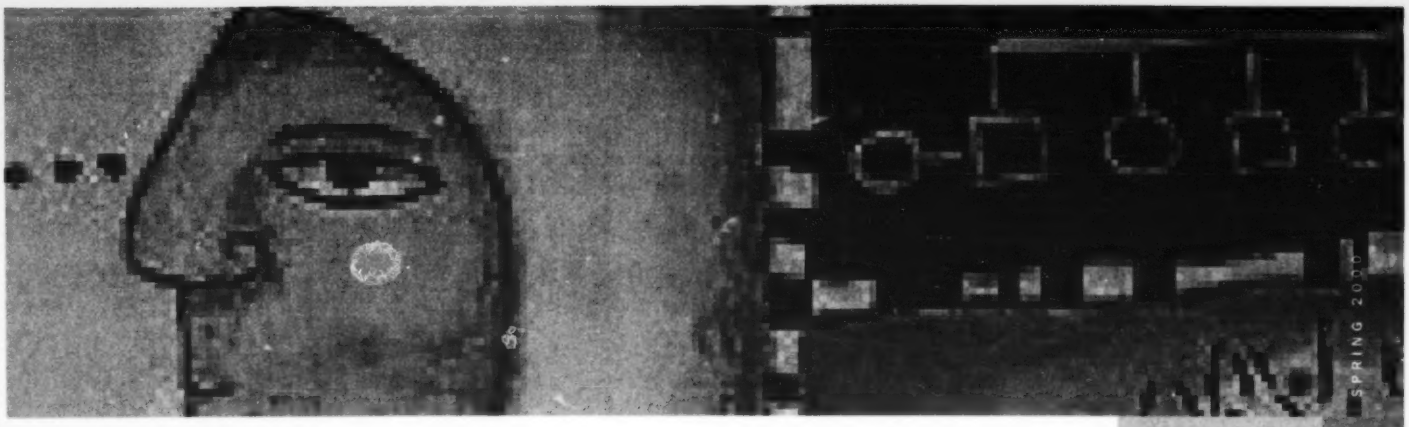
How gene therapy works

Gene therapy replaces faulty or missing genes with healthy genes in the cells. Genes produce proteins that help the cells work properly. When a gene is defective, it can cause diseases such as cancer, where cells divide and grow uncontrollably.

Gene therapy falls into two categories: germ-line cell therapy, where reproductive cells (eggs and sperm) are altered, and somatic cell therapy, where non-reproductive cells (brain cells and other body cells) are altered. Germ-line therapy is considered controversial because the genetic changes scientists make could be passed on to a patient's future children. Somatic cell therapy affects only the patient who receives the treatment. It's the only kind of gene therapy currently being tested on patients.

Research in Alberta

In Alberta, gene therapy research is still in its early stages, says Dr. Norman Wong, who chairs the Gene Therapy Research



committee at the University of Calgary.

The U of C has devoted 800 square feet of space to a gene therapy lab that Dr. Wong hopes will be equipped and operational within two years. Dr. Dan Muruve is helping to get the gene therapy lab up and running. "We hope the lab will become a national centre for molecular and gene therapies," he says. "It will be a place where we can develop and test experimental protocols before we try them out on patients."

The first and only gene therapy clinical trial in the province was approved in Edmonton in 1997: Dr. Lung-Ji Chang and his University of Alberta colleague Dr. Ken Petruk developed the treatment for brain cancer patients.

Dr. John Elliott is among the scientists at the University of Alberta who use gene therapy techniques in their research. Some of the work in his lab involves trying to develop new types of early blood tests for Type 1 diabetes mellitus (DM) and for multiple sclerosis (MS). Dr. Elliott has helped create a "designer mouse" whose immune system is very similar to that of someone with DM or MS. These mice help him find the correct peptides for his blood tests. Such early detection techniques may make it possible in the future to develop drugs that could block the progression of the two diseases.

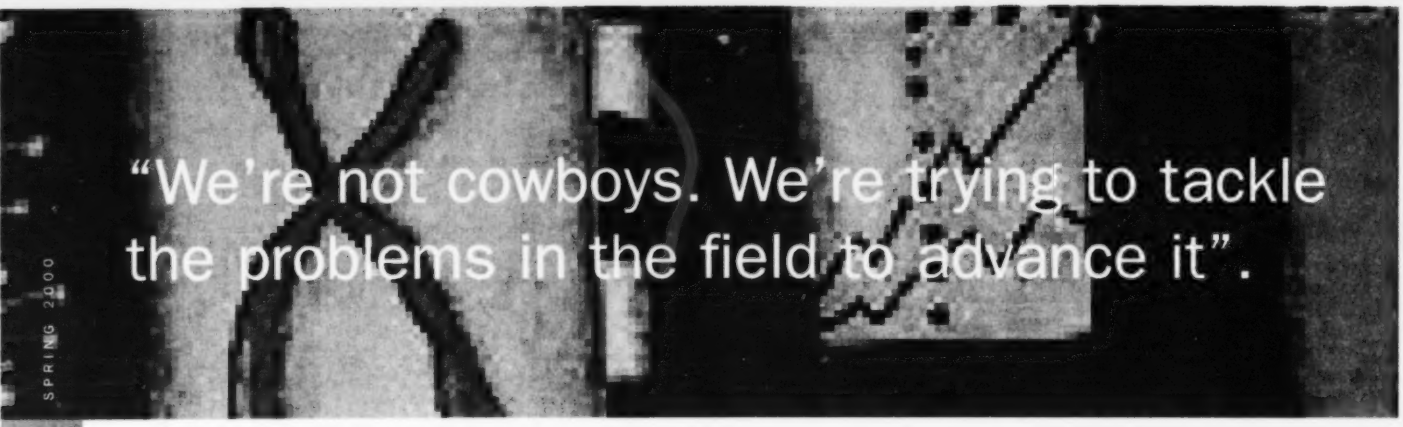
DR. JOHN ELLIOTT

Gene-maker

Dr. Irene Wanke is a researcher and doctor who specializes in endocrinology. Like her colleague Dr. Elliott, she has seen first-hand the severe, long-term side-effects such as blindness and heart disease, that patients with Type 1 diabetes mellitus can suffer. Dr. Wanke is working to genetically engineer the liver as a new source of insulin. Normally produced by pancreatic tissue, insulin is a hormone that helps the body use blood sugar. Type 1 diabetes destroys the pancreatic tissue that makes this hormone. Patients must take multiple daily injections of insulin to prompt their bodies to regulate the levels of their blood sugar. When Dr. Wanke's artificial gene is injected into the liver of diabetic rats, it makes insulin and lowers their blood-sugar levels.

DR. IRENE WANKE

While her results are promising, Dr. Wanke is now contending with a common problem encountered by gene therapy researchers: the body's mystifying rejection of artificial genes. In ongoing research, including collaborative work with scientists at the University of Florida, Dr. Wanke is trying to find a way to give staying power to the gene she's made. At present, it works for only two weeks in the liver. "I think this technique has huge potential, even though pancreas transplants and even islet transplants are gaining favour for the treatment of diabetes. One of the major limitations with those treatments is in getting a sufficient supply of islets and pancreata," Dr. Wanke explains. "Once it's



developed I think gene therapy will be very feasible for large numbers of people. It certainly would afford diabetics a better quality of life and, hopefully, prevent complications linked to the disease."

Genetic tool-builder

Dr. Derrick Rancourt was recruited to the University of Calgary to establish a provincial facility where scientists could use germ-line cell gene therapy to make transgenic mice. Engineered genes are implanted or genes disrupted in these specially modified mice (called "knock-in" or "knock-out" mice). These mice can then be used to test many research ides, including gene therapy techniques. Dr. Rancourt's lab can customize these genetic tools for fellow researchers by modifying particular genes in germ-line cells. For example, he has built transgenic mice that carry a mutation in one of the genes that cause retinitis pigmentosa, a leading cause of blindness in humans. "Any time a new human gene is discovered, researchers can test its effects using transgenic mice," Dr. Rancourt explains. "This technology is useful for studying the causes and effects of human diseases in addition to figuring out how genes work."

DR. DERRICK RANCOURT

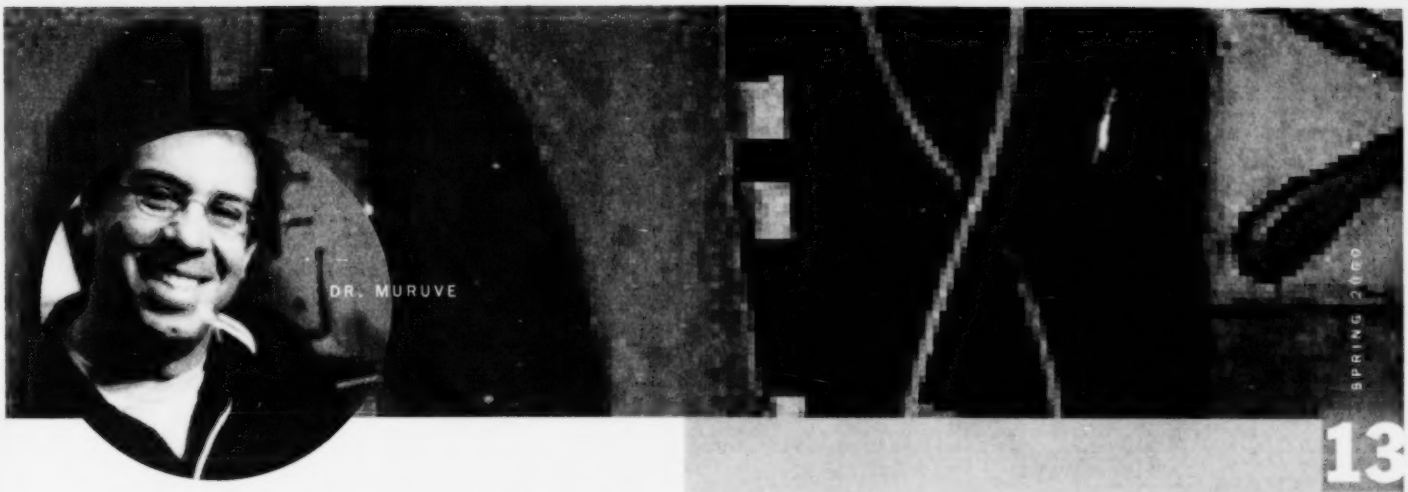
Genetic couriers

Viral vectors are one way scientists deliver healthy genes to targeted cells. Herpes, adenovirus, adeno-associated virus, and the retrovirus are four viruses primarily used as the vehicles to carry genes to the cells. Scientists such as Dr. Muruve, who specializes in somatic gene therapy research, alter vectors made of these viruses by removing the genes that cause dangerous infections and replacing them with the healthy genes they want to put into the cells. "Viruses are an ideal way to get new genes into the cells because viruses live by invading and transferring their genes to other body cells," he says.

Dr. Muruve is striving to find what he calls "the ultimate" viral vector in the adenovirus, a mutated cold virus. He wants to better understand how it works and how it can be engineered to safely and efficiently transfer genes to its targets without making patients sick—or possibly killing them.

The potential harm that viral vectors can inflict has been graphically illustrated in recent months. A teenage boy participating in a gene therapy clinical trial in the United States experienced a violent immune reaction, and later died after he was injected with an adenovirus that was being used to carry a particular gene to his liver. A seriously ill Canadian man also died after undergoing gene therapy treatments. "The viruses we work with are made less lethal before they're given to patients, but they can still be extremely harmful," Dr. Muruve cautions. "We need to keep studying the properties of viral vectors to understand what their impact will be on the body, to lessen the damage they cause, and to ensure they are safe to use on patients," he emphasizes.

Scientists have two other ways of getting genes where they need to go. They can coat particles of gold or tungsten with



DNA and then blast into targeted cells with gene guns. Or they can use microinjection, a technique where tiny needles inject genes into specific cells.

Risks and gains

Alberta researchers are optimistic about the future of gene therapy, but they take a cautious approach to the prospect of human testing. "Personally, I feel that gene therapy is very much in its infancy," Dr. Wanke says. "I think it has huge potential, but presently we just don't have treatments that are safe for clinical trials." As for the potential of her own research, she has this to say: "I don't want to raise false hope. While our findings are very exciting, we still need to do far more work in the laboratory to ensure that we have something that is feasible and not harmful before it's tested on patients."

Dr. Muruve concurs. "We're not cowboys. We're trying to tackle the problems in the field to advance it," he says.

Dr. Irene Wanke is a Heritage Clinical Investigator and an Assistant Professor in the Department of Medicine in the Faculty of Medicine at the University of Calgary.

Dr. Dan Muruve is a Heritage Clinical Investigator and an Assistant Professor in the Department of Medicine in the Faculty of Medicine at the University of Calgary.

Dr. Norman C.W. Wong is a Heritage Scientist and a Professor in the Departments of Biochemistry and Molecular Biology in the Faculty of Medicine at the University of Calgary.

Dr. John Elliott is a Heritage Senior Scholar and an Associate Professor in the Department of Medical Microbiology and Immunology in the Faculty of Medicine and Dentistry at the University of Alberta.

Dr. Derrick Rancourt is a Heritage Scholar and an Assistant Professor in the Departments of Oncology and Biochemistry and Molecular Biology in the Faculty of Medicine at the University of Calgary.

Sidebar Heading

A team of University of Alberta scientists that includes Dr. John Elliott is pioneering research to achieve insulin-free diabetes using islet-cell transplants (islets produce insulin). Two factors stand in their way. The first is the limited availability of islet tissue, which is harvested from organ donors who are limited in number. The other obstacle is the body's rejection of transplanted tissue. Transplant recipients must take high daily doses of immunosuppressant drugs to fight rejection. To combat these problems, the team may turn to the barnyard. Pigs, which have organs similar in size and function to humans, may be the solution. In lab experiments, pig islet tissue has proven to reverse diabetes in mice.

The researchers may use gene therapy to find a way to block the human body's rejection of pig islet tissue. They could develop a designer pig containing one or more molecules that would turn the immune system off, says Dr. Elliott. "In the future, we could produce barnyards of pigs that were being produced just to make islets to treat diabetes," he suggests. It costs about $500,000 to make one transgenic pig. But the announcement in March that PPL Therapeutics plc (the commercial firm responsible for Dolly the Sheep) had cloned five piglets, may eventually provide scientists with a cheap and endless supply of designer pigs, comments Dr. Elliott. He already has a formal collaboration with the Scottish-based company.

Understanding the "disease that

If only ovarian cancer made more noise. But this "disease that whispers" tends to go unnoticed until it has spread beyond the ovary. And that makes ovarian cancer deadly. Only about 50% of women with ovarian cancer are alive five years after their diagnosis—one of the highest death rates of any cancer. In contrast, women diagnosed with breast or uterine cancer have a five-year survival rate of about 85%.

"Early detection vastly improves survival for breast and uterine cancers," says Heritage cancer researcher Dr. Linda Cook. "Early breast cancers can be detected through mammography. Unusual vaginal bleeding often leads to the identification of early uterine cancers. But there is a frustrating lack of overt physical symptoms in early ovarian cancer.

"Consequently, there is a real need for a cost-effective highly predictive test for ovarian cancer. But we simply don't know what to test for because the causes of ovarian cancer are unclear. We need to understand much more about how and why this disease takes hold."

In order to answer some of the questions, Dr. Cook has teamed up with other scientists to try to identify early changes in ovarian tissue that might progress to cancer. The multidisciplinary group includes cancer epidemiologists, pathologists, molecular biologists and oncologists.

Their first step will be a one-year pilot project involving Edmonton- and Calgary-area women who have had at least one ovary surgically removed. If they agree to participate, the tissue from the removed ovary will be tested for molecular changes. As well, interviews with the participants will be used to determine what genetic or environmental factors may have contributed to their risk for ovarian tumours.

The project will look at three groups of women: women with benign ovarian tumours (also called ovarian cysts), those with borderline tumours, and those with invasive ovarian cancer.

The pathologists on the team will study the ovarian tissue for changes in certain genes that are linked to the development of cancer. The epidemiologists will interview participants about their reproductive history, lifestyle, and environmental exposure. There are some known risk factors for ovarian cancer such as family history of ovarian, breast or colon cancer,

"There is a frustrating lack of overt physical symptoms in early ovarian cancer."

whispers"

never having children, a history of infertility, early menstruation, late menopause, and increasing age.

"In our study, we're looking back to see what risk factors apply to these women, and we're looking at the tissue itself. We'll see if we can relate the two," explains Dr. Cook.

Information on molecular changes, especially early changes before cancer fully develops, could be the basis for a new early-detection screening tool. And if early changes in ovarian cells are related to any of the risk factors, this information could be used to develop prevention strategies.

With the pilot study set to begin April 1, the researchers are already looking ahead to a full-scale project. The long-term goal is to go Alberta-wide with a multi-year study, perhaps including another province.

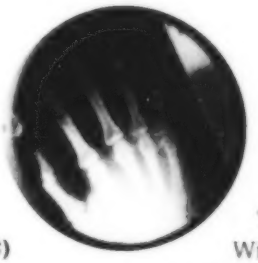
"I've always wanted to do a study like this but I didn't have the opportunity until I came to Alberta in 1998," says Dr. Cook. "It was a delightful surprise to come here and find that so many people wanted to do collaborative work in this area.

"There's great potential that the information we collect will give us new and important clues to the cause of ovarian cancer. And we really could find something that's highly predictive, which would make early screening for ovarian cancer possible. We could turn a corner on this disease."

Dr. Linda Cook is an AHFMR Population Health Investigator and research scientist with the Alberta Cancer Board's Division of Epidemiology, Prevention and Screening at the University of Calgary. She also receives support from the Medical Research Council of Canada. The team members are Dr. Anthony Magliocco, University of Calgary, Dr. Louis Honoré, University of Alberta, and Dr. Gavin Stuart, Tom Baker Cancer Centre.

A new look for x-rays

"Did you bring your x-rays with you?" asks the receptionist at the doctor's office. If you don't have that large manila envelope, you know you've got a problem.



But things are changing. Carrying around your own x-rays may soon be a thing of the past if a Calgary company has its way. With help from AHFMR, Imaging Dynamics Corporation (IDC) has developed a filmless x-ray system. Instead of producing x—rays on conventional film, the images are recorded digitally in a computer file and viewed on a monitor. They can be sent over phone lines from office to office.

IDC's Xplorer 1000 system has been in development and clinical trials for about eight years. In March of this year, the company achieved a major milestone with its first commercial installation at the Calgary Center for Health. Production and marketing are now in high gear.

A better way to x—ray

All this activity seems almost unreal to the Xplorer's inventor, Robin Winsor. "For years I've focused on designing and improving the system. It's exciting to see it finally in commercial use," he says.

film

A new business venture wasn't even a remote consideration when Mr. Winsor first came up with the idea. The spark was a dinner conversation. Mr. Winsor, a geophysicist, and his wife, a veterinarian, were having dinner with a couple of friends, also vets.

"I'm really interested in technology and I was talking about using image processing on x—rays to get better quality pictures," he recalls. "My wife and her colleagues weren't at all interested. But when I talked about how I could make the x—ray process faster by using a digital system, I got their attention right away."

So Winsor bought himself a digital camera, banged together some plywood for a frame and –Voila! – had his first prototype in a few weeks. "Although it was a rudimentary system, it was pretty clear that this design would cost much less than the digital systems on the market," he says. "It was worth pursuing."

Indeed. Even after using materials considerably more high-tech than plywood, one of the advantages of IDC's Xplorer system remains its price—about one-third to one-tenth the cost of other digital systems. At the same time, the system delivers high-quality images with resolution, contrast and clarity equal to film x—rays, or better. It generates the images within seconds, compared to 10 minutes or more for developing x—ray film.

Unlike many other digital systems, the Xplorer 1000 works with existing x—ray generators. It's an optical system in which the x—rays are converted to

A digital image requires a single image, reducing the number of x-rays and therefore the radiation dose received by the patient.

visible light by a phosphor screen, and a lens and mirror transfer the image to a digital camera. The data is then sent to a regular office computer for viewing with image-processing software.

IDC owns patents related to this technology. The patents cover the approach to generating filmless x–ray images, as well as methods of use in markets that include medical, veterinary, security, and non-destructive testing. The company is certified to market the device in Canada and has applied for FDA approval to market in the United States.

The move to digital

Although other medical imaging techniques, such as ultrasound, computerized tomography (CT), and Magnetic Resonance Imaging (MRI) have gone to a digital format, x–rays have lagged far behind. This is changing however, as the advantages of digital technology become widely appreciated.

Cost is a prime factor driving the move to digital. Expenses add up with "hard copy" x-rays because they require film developers, processing chemicals, and a lot of storage space. Another factor is that film can be in only one place at one time. If a specialist needs to see an x–ray, the film must be sent by courier. The process takes time and often delays a diagnosis.

For radiologists who interpret x–rays, digital images offer a key advantage because they capture more information than film does.

"A digital image is not simply electronic paper–it provides one thousand times more information than film," explains Mr. Winsor. "By changing the grey level of the image, bones, soft tissue and even metal and plastic parts such as artificial hipbones can all be viewed from a single image. To get similar detail on film requires using multiple x–rays, which substantially increases the radiation dose received by the patient."

"The market is ready for digital x–rays," says Harvey Brovald, IDC's Sales and Marketing Vice-President. "For example, the theme of the annual meeting of the Radiological Society of North America (RSNA) in 1999 was 'going digital'. We don't have to convince people that digital is a good thing. Our task is to convince them that our system is the best."

IDC's efforts to commercialize the Xplorer system have been aided by AHFMR's Technology Commercialization (TC) program. It awarded IDC $150,000 to assist with technical issues and the development of a business plan.

"The funding from AHFMR was critical," notes Mr. Brovald. "We were close to commercialization, but not at a stage where we could attract investors. It was essential to bridge this gap. Now, other forms of financing are available. In fact, we recently completed a $9 million financing that will see us through the commercialization of the current product line.

"But without the TC money, we might not have made it to where we are today."

IDC's initial target markets are new radiology centres and those that are expanding or retrofitting. Hospitals are another big market, but they tend to have established relationships with large vendors. IDC will first try to break into niche areas such as x–rays through casts to see how bones are healing. (For a film-based x–ray, the cast must be removed.)

And after that?

"Maybe we'll even see the Xplorer in my wife's veterinary office," says Mr. Winsor with a smile. He enjoys his new role as IDC's Chief Technical Officer, in charge of developing new applications for the digital x–ray system. One of these is in mammography and involves using a computer program to scan for abnormalities on the x–ray image.

"I'm a techie, not a businessman. I'm returning to my roots," says Winsor. "At the beginning, I didn't think the business side through very well. And that certainly caused some missteps early on. But we now have a team of people who are very capable of handling the technical, financial, administrative and marketing aspects of this business. We're on solid ground."

Imaging Dynamics Incorporated received $150,000 in funding from AHFMR's Technology Commercialization Program.

Seeking the painful truth

Rheumatologist **Dr. Liam Martin** has treated all sorts of painful joint and muscle problems in his patients over the past 20 years. One of the most interesting for him is fibromyalgia, the unexplained chronic pain condition that affects an estimated 2%-4% of the population. The vast majority of victims are women. Fibromyalgia continues to baffle scientists, doctors, and patients because it doesn't have a pathological pathway; that is, x—rays and blood tests don't reveal any abnormalities.

Recently, Dr. Martin completed an AHFMR-supported research project that assessed the role of exercise in the management of fibromyalgia. The results were encouraging. Patients who participated in a specially designed exercise program, with or without an education component, reported an improvement in their symptoms.

As the exercise project was drawing to a close, Dr. Martin had a conversation that laid the groundwork for a new avenue of study of fibromyalgia. His colleague, attention deficit disorder (ADD) specialist and Heritage researcher Dr. Bonnie Kaplan, related that one of her associates had reported relief from fibromyalgia after taking a particular nutritional supplement that was being studied in attention deficit disorder. Intrigued, Dr. Martin and Dr. Kaplan decided to test the product on fibromyalgia patients in a research study.

The project is a double-blind, placebo-controlled study, meaning that neither the researchers nor the study volunteers know whether the product or the placebo is being given. The volunteers have to meet the criteria for fibromyalgia* as formulated by the American College of Rheumatology. The researchers hope to enroll a total of 120 patients from the Calgary area in the two-year study. "A 20% improvement would be considered positive results," he says, adding that patient questionnaires will be the main tool used to assess improvement.

"The reason we started to work with this supplement is because people came to us reporting relief when they used it. Our goal is to try and determine if it does indeed work and then identify the active ingredients are that are helping," says Dr. Martin. He can't name the product but does say the nutriceutical company is a reputable one and that the supplement has small amounts of minerals and anti-oxidants, although it's "more than a multivitamin".

Dr. Liam Martin is a rheumatologist and a researcher whose project on fibromyalgia is supported by the Health Research Fund, which is administered by AHFMR on behalf of Alberta Health and Wellness.

Looking through the Adoles

It's the age that strikes fear into every parent's heart. **Adolescence ...** the time of experimentation with new ideas, new friends and, unfortunately, new risk behaviours such as smoking, drinking, taking illicit drugs and having sex.

Today, a substantial minority of young people run very serious health risks. Canadian data show the major risk period for initiation into alcohol, tobacco and most illegal drugs begins around age 12 and is mostly finished by 22.

As a result, many health researchers call early adolescence the "window of vulnerability" for life-threatening health risks. By the ages of 16 to 18, this vulnerability is strongly established for those who emerged as vulnerable in early adolescent years.

But what makes a child vulnerable? That's one of the questions being investigated by a team of researchers from the University of Alberta, the Capital Health Authority and the Alberta Alcohol and Drug Abuse Commission (AADAC). Their AHFMR-supported study is designed to collect key data on physical and emotional health risks for Alberta adolescents and relate them to the process of identity formation in young people.

"Our team is focused on practical outcomes," says Dr. Brenda Munro, a Professor in the Department of Human Ecology at the University of Alberta. "By understanding who is vulnerable and why they are vulnerable, we can move forward in designing programs that reach these children effectively."

It's this emphasis that particularly interests AADAC, says Mr. Gord Munro, AADAC's Research and Special Projects Coordinator. "On a daily basis AADAC deals with adults who have serious addictions. We develop and implement programs to help them, but we've always wondered if we can't tackle these problems earlier. This study will help us understand the issues that are important in junior and senior high."

And do something about them, adds Dr. Maryanne Doherty, a Professor of Secondary Education at the University of Alberta.

"My interest is in curriculum development and teacher education," she says. "We know students have fairly detailed knowledge about health risks, good attitudes and good intentions. But for many kids, something happens. What are the intervening variables? What can we do, as teachers, to help?"

AADAC personnel who deal with adults with serious addictions would like to tackle these problems earlier, when people are in junior or senior high school.

"window of vulnerability"

cence

The research involves two major questionnaires and personal interviews. The first questionnaire, administered to 2000 students in junior and senior high schools across Alberta in the fall of 1999, dealt with mental health issues. The second survey, completed in the spring of 2000, asked questions about education, eating, body image, addictive behaviour, and relationship with parents. The third component is a series of focus groups and one-on-one interviews with selected young people from various ethnic groups and risk categories.

One of the unique features of this study is its focus on identity and using identity to understand health behaviour choice. While identity formation begins in childhood, adolescence accelerates the process. It is a time of intense experimentation with roles, behaviours and values. Through this process, adolescents arrive at an identity that includes certain health-related behaviours and mood states that may be hard to change, if necessary, later on.

The study is also designed to look at risk behaviours in ethnic groups. Identity development can be particularly complicated for adolescents belonging to ethnic groups. These young people are often caught between their parents' ethnic beliefs and values, and those of mainstream society.

Survey results are now being analyzed and the team hopes to have preliminary results by the fall of 2000.

"Everyone on the research team is excited about the results and how to use them in our own areas," says Dr. Joy Edwards, a Public Health Research Scientist with the Capital Health Authority. "From the public health perspective, we'll have invaluable data about the health of our young people and key information that will help us design programs and policies aimed at reducing health risks.

"We'll be able to do things that really make a difference."

Details on the team:

Dr. Gerald Adams, *University of Guelph*
Dr. Maryanne Doherty, *University of Alberta*
Dr. Joy Edwards, *Capital Health Authority*
Dr. Brenda Munro, *University of Alberta*
Mr. Gord Munro, *Alberta Alcohol and Drug Abuse Commission*

Names of graduate students are coming...

Dr. Brenda Munro's project is supported by the Health Research Fund, administered by AHFMR on behalf of Alberta Health and Wellness.

10,000 km Away from Home

Dr. Peter Ferdinandy is one such scientist. A medical doctor who is also a cardiac researcher from Szeged, Hungary, he was a faculty member at the Albert Szent-Györgyi University Medical School when he decided to pursue further basic biomedical research. Heritage researcher Dr. Richard Schulz brought Dr. Ferdinandy to Edmonton in 1997 on a two-year AHFMR Post-doctoral Fellowship.

Dr. Ferdinandy wrote about his experiences in Alberta in the December 1999 newsletter of the International Society for Heart Research. The following is an excerpt from his article.

In 1997, I suddenly realized that, at the age of 30, I was consumed with writing grant applications, papers, and reports, and the network of university and industrial collaborators. I felt I had to escape somewhere, go back to the laboratory bench, and get some new scientific input. But where? I wanted to go to a very good cardiac research lab with a focus on nitric oxide (NO, an essential molecule in the body), a good biochemical and pharmacological background, an exciting scientific atmosphere, and a project that would be aimed at a real clinical problem. One might think that a lab like this does not exist on planet Earth. But a friend informed me that Dr. Richard (Rick) Schulz from the Cardiovascular Research Group at the University of Alberta was looking for a post-doctoral fellow.

With the support of fellowships from the Medical Research Council of Canada and the Alberta Heritage Foundation for Medical Research, and with three connecting flights, my family moved to Edmonton—only 10,000 kilometres away from home!

The laboratory on the fourth floor of the Heritage Medical Research Centre Building was my dream laboratory. The building (very close to the

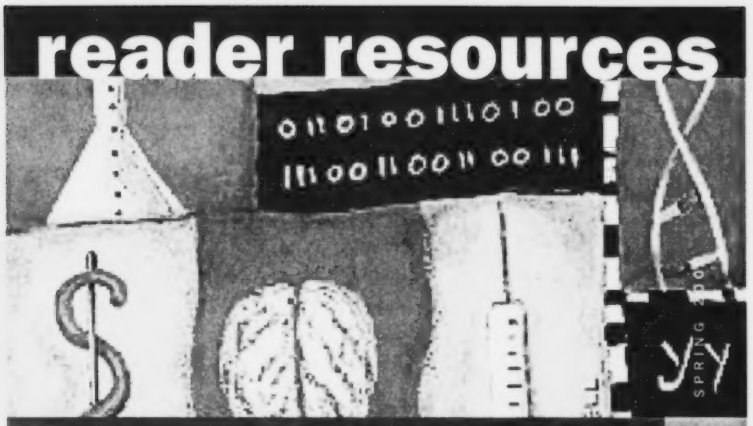
river valley) looks like the Pompidou Centre in Paris, France. Rick Schulz, a recognized cardiovascular nitric oxide-peroxynitrite expert, was a very helpful supervisor and a good friend. There are other world-class scientists, like Heritage researchers Gary Lopaschuk and Alex Rabinovich, next door.

The project I worked on was very exciting. We wanted to have clear-cut evidence about the involvement of peroxynitrite (a toxic substance formed from certain metabolic processes) in heart damage during heart attacks, something that previous studies had not been able to prove. After two years we succeeded, and in June of 1999 I was awarded the Young Investigators Award at the meeting of the European Section of the International Society for Heart Research in Maastricht, the Netherlands.

In summary, I had a great time in Edmonton during my Heritage Post-doctoral Fellowship. I received a lot of new scientific input; the number of my kids increased by one with a new Canadian-born baby boy; and my two older kids speak great Canadian English. I am back in my lab in Szeged now, and we have already planned a long-term collaboration with Rick Schulz. We will probably compare the effects of the minimum and maximum temperatures in January and July in both Edmonton and Szeged on the effectiveness of cardiovascular research projects to find out finally why I got my award!

Dr. Peter Ferdinandy was a AHFMR Post-doctoral Fellow in Heritage researcher Rick Schulz's laboratory from 1997 to 1999. Dr. Ferdinandy is a cardiologist at the Albert Szent-Györgyi University Medical School is Szeged, Hungary.

reader resources



Research Views
Dr. Michael Smith and the genetics revolution

Genome Sequence Centre, B.C. Cancer Agency, Vancouver
http://www.bcgsc.bc.ca/

Centre for Integrated Genomics, part of the B.C. Cancer Agency
http://www.cigenomics.bc.ca/eng/resact.htm

$43 Million for AHFMR research

www.ahfmr.ab.ca

A new crystal ball
The ethics of genetics use

Health Law Institute, University of Alberta
http://www.law.ualberta.ca/centres/hli/index.htm

Gene therapy

Industry Canada
Gene therapy overview
http://strategis.ic.gc.ca/SSG/tc00029e.html

Oncolink
National Cancer Institute
Questions and answers about gene therapy
http://oncolink.upenn.edu/pdq/600718.html

Understanding the "Disease that Whispers"

Ovarian Cancer Alliance Canada
http://www.ocac.ca/

Health Canada
Ovarian Cancer Canada
http://www.hc-sc.gc.ca/hpb/lcdc/bc/updates/ovar_e.html

Cancer Information Services
Web site:
http://www.cancer.ab.ca/cis/cismain.htm

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Northern Aboriginal Languages: 1-888-261-4673

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fibromyalgia

Web sites:
American College of Rheumatology
*Criteria for fibromyalgia
http://www.rheumatology.org/patients/factsheet/fibromya.html

What is fibromyalgia?
http://www.rheumatology.org/patients/factsheet/fibromya.html

Looking through the "window of vulnerability"

Alberta Alcohol and Drug Abuse Commission
http://www.gov.ab.ca/aadac/index.html

10,000 km from home

Dr. Peter Ferdinandy invites visitors to his web site at:
www.cardiovasc.com

Two Decades of Success

The AHFMR Timeline to 2000

1980

An Act of Legislature creates AHFMR, with an endowment of $300 million, and the Board of Trustees is established. Funding for students and fellows is initiated.

1985

One of Canada's first Technology Transfer Programs is established to help researchers and private industry take innovations from the lab to the marketplace.

The 5000th application is processed, 130 senior scientists are in place, and more than 1000 university students have been supported.

1987

The first International Board of Review applauds the Foundation's outstanding success. AHFMR research buildings open at the U of A and the U of C. More than 2000 students and researchers-in-training have been supported.

1993

The second International Board of Review affirms AHFMR's leadership in supporting medical research in Canada with effective and often innovative granting programs. The IBR verifies that many Foundation scientists are earning international acclaim for their discoveries.

1997

$15 million is allocated to the new AHFMR Opportunity Fund that matches funds for strategic research infrastructure initiatives in the province. This is one of many ways AHFMR programs complement rather than duplicate provincial and national programs.

1998

The third International Board of Review declares that AHFMR's "solid commitment to excellence" has nurtured a superlative scientific community which garners much scientific acclaim, and that much of this success stems from the Foundation's arms-length relationship. The Board also notes the economic spin-offs, outside research dollars being attracted to Alberta Universities, and significant job creation

2000

AHFMR's success inspires the Government of Alberta to create the Alberta Heritage Foundation for Science and Engineering Research, modeled on AHFMR.

172 researchers are supported, and the endowment is valued at $1 billion. The cumulative total of AHFMR funding reaches $600 million.